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10/728,323	12/04/2003	Michael J. Caplan	2002834-0232	8163

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 09/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,323	CAPLAN, MICHAEL J.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-44* is/are pending in the application.

4a) Of the above claim(s) *37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36 and 38-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/4/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/8/05; 1/27/05; 12/6/04; 4/3/04; 2/2/04; 12/4/03*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Claims 34-44 are pending.

2. Applicant's election with traverse of Group 1, (Claims 34-36 and 38-44) drawn to a composition comprising dead E coli containing therein at least one modified allergen differs from that of a wild-type allergen, the modified allergen differs from that of a wild-type food allergen wherein the wild-type allergen is peanuts, and a pharmaceutical acceptable carrier, filed 7/7/05, is acknowledged. The traversal is on the grounds that despite making this election without traverse, applicant submits that related generic claims have already by search in parent application 09/731,375 and applicant has provided with a number of prior art references in the parent application and again in this divisional filing. This not found to be persuasive as each application is examined on its own merit. The volume of prior art references supports the examiner's position that just the prior arts alone is a burden to examine more than one invention. This is not found persuasive because of the reasons set forth in the restriction mailed 5/18/05. Further, a prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement of Group 1 and Groups 2-9 is still deemed proper and is therefore made FINAL.

3. Claim 37 is withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

4. Claims 34-36 and 38-44, drawn to a composition comprising dead E coli containing therein at least one modified allergen differs from that of a wild-type allergen, the modified allergen differs from that of a wild-type food allergen wherein the wild-type allergen is peanuts, and a pharmaceutical acceptable carrier, are being acted upon in this Office Action.

5. Claims 35-36 are objected to as the claims encompass non-elected embodiments.

6. The disclosure is objected to because incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation

by reference. Therefore the embedded hyperlinks and/or other forms of browser-executable code disclosed on pages 6, line 2 and page 8, line 18 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 34-36 and 38-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification discloses only a composition comprising heat-killed *E. coli* containing therein peanut allergen comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3 (see page 33 of specification). However, the amount of allergen produced on a per cell basis varied depending on which clone tested. In general, more Ara h3 was produced than Ara h2 and Ara h1. The specification discloses the intended use of the claimed composition is to treat or prevent allergic reactions in a mammalian subject. The specification discloses mice injected with *E coli* fails to produce any detectable levels of Ara h1 specific IgG which is critical for converting a Th2 immune response to a Th1 immune response as a method of treating or preventing peanut allergy in a subject (See page 34 of specification). Furthermore, mice immunized with *E. coli* that makes Ara h2 produce high levels of IgG1 (indicative of Th2 immune response) and IgG2a (indicative of Th-1 type immune response), which again fails to modulate the host immune response to peanut allergen Ara h2 toward Th1 type response. Finally, mice immunized with *E. coli* that makes Ara h3 produce high levels of IgG2a (indicative of Th-1 type immune response) and low levels of IgG1 (indicative of Th2 immune response).

The specification does not teach how to predict which composition comprising which heat-killed *E. coli* is useful for preventing or treating peanut allergy. The specification does not teach how to make any composition comprising dead *E coli* containing therein any one or more modified allergens whose amino acid sequences differ from that of any "wild-type" allergens such as any foods allergen, or any peanut allergens that "occur in nature" such that the modified allergens have a reduced ability to bind to or cross-link IgE as compared to any wild-type allergen and a pharmaceutical acceptable carrier. This is because of the lack of guidance as to which amino acid(s) within the full-length sequence and the corresponding IgE binding site of any naturally occurred allergens to be modified by substitution, deletion, addition and/or combination thereof such that the modified allergens have a reduced ability to bind or crosslinked IgE compared to the naturally occurring wild-type allergens when expressed in *E coli*. Further, the specification does not teach the "portion" containing IgE binding site of all naturally occurring allergen to be deleted. There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Fasler *et al* teach that allergen peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2 and IFN-γ production which is indicative of Th1 immune response. Fasler *et al.* further teach that substituting a neutral amino acid residue such as Asn at position 173 with either a basic Lysine, which is a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al* teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al* teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Kleber-Janke et al teach the unpredictability of bacterial E coli expressing allergen such as peanut allergens Ara h1, Ara h2, Ara h5 and Ara h6. The amount of allergen expressed in E coli depends on the strain of E coli such as BL21(DE3), the effect of rare codon usage among the peanut allergens (see page 421, col. 2, in particular). Kleber-Janke et al teach Ara h1, Ara h2, and Ara h6 are affected by poor codon usage. Given the unlimited number of undisclosed modified allergen, modified food allergen and modified peanut allergens, it is unpredictable which composition comprising dead *E coli* strain containing any modified allergen would be useful for treating or preventing allergy in mammalian subject.

Even if the allergen is limited to unmodified peanut allergen Ara h1 (SEQ ID NO: 1), Ara H2 (SEQ ID NO: 2) and Ara h3 (SEQ ID NO: 3), immunizing mice with dead *E. coli* contained therein three different peanut allergens results in three different outcomes. Since the modified allergens contained within the *E coli* is not enabled, it follows that any modified allergen is located in the cytoplasm or periplasm of the dead E coli in the claimed composition is not enabled. It also follows that the composition recited in claims 43 and 44 is not enabled.

In *re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

9. Claims 34-36 and 38-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for any composition comprising any *dead E. coli* containing therein at least any one or more modified allergen, any modified allergen such as any modified food allergen, any modified peanut allergen whose amino acid sequence differs from the naturally occurring wild-type allergen that occurs in nature having one or more amino acid deletions, substitution, or addition within any IgE binding site, or any portion of any wild-type allergen sequence deleted such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the wild-type allergen; and a pharmaceutically acceptable carrier.

The specification discloses only a composition comprising heat-killed *E. coli* containing therein peanut allergen comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3 (see page 33 of specification). However, the amount of allergen produced on a per cell basis varied depending on which clone tested. In general, more Ara h3 was produced than Ara h2 and Ara h1. The specification discloses the intended use of the claimed composition is to treat or prevent allergic reactions in a mammalian subject. The specification discloses mice injected with *E coli* fails to produce any detectable levels of Ara h1 specific IgG which is critical for converting a Th2 immune response to a Th1 immune response as a method of treating or preventing peanut allergy in a subject (See page 34 of specification). Furthermore, mice immunized with *E. coli* that makes Ara h2 produce high levels of IgG1 (indicative of Th2 immune response) and IgG2a (indicative of Th-1 type immune response), which again fails to modulate the host immune response to peanut allergen Ara h2 toward Th1 type response. Finally, mice immunized with *E. coli* that makes Ara h3 produce high levels of IgG2a (indicative of Th-1 type immune response) and low levels of IgG1 (indicative of Th2 immune response).

The specification does not describe the structure corresponding with function of any modified allergen in the claimed composition. There is a lack of a written disclosure about the structure of any and all modified allergen, modified allergen such as any food allergen, any modified peanut allergen whose amino acid sequence is identical to that of said allergen protein as it occurs in nature except that at least one or more amino acids have been deleted, substituted, added within any IgE binding site so that the modified protein has a reduced ability to bind and crosslink IgE antibodies. Without the amino acid sequence of any modified allergen in the claimed composition, the specification merely ask one of skilled in the art to come up with the structure of the modified allergen in the dead *E coli* for the claimed composition. Further, given

the lack of a written description of *any* additional representative species of modified allergens other than the specific modified peanut allergens in *E coli* that produces any modified allergen protein as encompassed by the claims, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "portion" in claim 40 is ambiguous and indefinite because "potion" could be as little as one amino acid or could be as much as 100 amino acids. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 34-36, 38-40, and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,888,799 (March 1999, PTO 1449) in view of WO 99/38978 publication (Aug 1999, PTO 1449) and Yeung et al (J Immunology

The '799 patent teaches a composition comprising live bacteria such as *E. coli* K-12 containing therein any to allergen and a pharmaceutically acceptable carrier to the mucosal immune system (See entire document, col. 2, line 25-34, col. 7, line 53, col. 9, lines 59-67, in particular). The reference allergen is located in the periplasm (See column 14, lines 31-35, in particular). The reference microorganism such as *E. coli* K-12 have the advantages of (1) being avirulent (derivative of a pathogenic strain) and do not exchange genetic material with the pathogenic strains, (2) useful as delivery vehicle to stimulate the host cellular response such as the production of IgA in the secretory pathway with a concomitant stimulation of the humoral and cellular immune response (See column 2, lines 60-64, column 5, Table 1, in particular).

The claimed invention as recited in claim 34 differs from the teachings of the reference only in that the composition comprising dead *E coli* containing therein at least one modified allergen whose amino acid sequence differs from that of a wild-type allergen that occurs in nature such that the modified allergen has a reduced ability to bind to or cross-link IgE as compared with the non-modified allergen.

The claimed invention as recited in claim 35 differs from the teachings of the reference only in that the composition comprising dead *E coli* containing therein modified allergen found in foods.

The claimed invention as recited in claim 36 differs from the teachings of the reference only in that the composition comprising dead *E coli* containing therein modified allergen found in peanuts.

The claimed invention as recited in claim 38 differs from the teachings of the reference only in that the composition comprising dead *E coli* containing therein modified allergen found in Ara h1 (SEQ ID NO: 1), Ara h2 (SEQ (ID NO: 2) or Ara h3 (SEQ ID NO: 3).

The claimed invention as recited in claim 39 differs from the reference from the teachings of the reference only in that the composition dead *E coli* containing therein modified allergen whose amino acid sequence differs from the sequence of wild-type allergen by one or more

amino acid amino acid deletions, substitution, or addition within an IgE binding site of the wild-type peanut allergen.

The claimed invention as recited in claim 40 differs from the reference from the teachings of the reference only in that the composition dead *E coli* containing therein modified allergen lacks a portion of the wild-type allergen within said portion includes IgE binding site.

The WO 99/38978 publication teaches a composition comprising live *E coli* containing therein at least one peanut allergen such as Ara h1, Ara h2 and Ara h3 where the amino acids within each of the binding sites have been substituted such that the modified allergens have reduced IgE binding compared with the wild-type (see page 3, line 22-30, page 10, line 10-16, page 16, line 22-33, in particular). The reference further teaches a method comprising the steps of providing a composition comprising a modified allergen such as peanut protein Ara h1, Ara h2, Ara h3 or a portion thereof wherein the protein or portion thereof has at least one amino acid has been deleted or substituted such that the modified protein has a reduced ability to bind and crosslink IgE antibodies (See Abstract, page 19, reference SEQ ID NO: 2, 4 and 6, claims 14, 17-20, 23 and 36 of WO 99/38978 publication, in particular). The reference modified peanut allergen is expressed or produced in a recombinant host such as bacteria wherein the allergen is secreted into the periplasma space since the bacterial cells must be lysed in denaturing binding buffer (See claim 27 of WO 99/38978 publication, page 16, lines 30-32, in particular). The WO 99/38978 publication further teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and substitution of a specific single amino acid within each of the identified epitope abolishes IgE binding (See abstract, page 18, Table 4, Table 5 and Table 6, in particular).

Yeung et al teach heated-killed bacteria such as listeria monocytogenes has innate adjuvant activity to provoke TH1 dominated immune response in treatment of allergy (see page 4146, col. 1, in particular). Yeung et al further teach heat-killed bacteria rather than live bacteria are effective in reducing antigen/allergen specific IgE synthesis (see page 4151, col. 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute live *E coli* comprising allergen as taught by the '799 patent for the lived E coli comprising modified peanut allergens such as Ara h1, Ara h2, Ara h3 or a portion thereof that has a reduced ability to bind and crosslink IgE antibodies as taught by the WO 99/38978 publication and heat-killed it and use it as an adjuvant in a vaccine to promote Th1-

dominated immune response as taught by Yeung et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 99/38978 publication teaches the critical amino acids within each of the IgE binding epitope of the peanut protein such as Ara h1, Ara h2 and Ara h3 that are important for IgE binding and the modified peanut allergens are useful for a method of treating a subject susceptible to an anaphylactic reaction (allergic reaction) to peanut allergen (See abstract, in particular). It is within the purview of one ordinary skill in the immunology art to heat-killed microorganism such as *E coli* as a vaccine as taught by the '799 patent or (see col. 1, lie 52-57, in particular) and serve as an adjuvant as taught by Yeung et al. Claim 43 is included in this rejection because it is obvious that the modified allergen cannot be detected by antibody binding without disrupting the dead E coli since the modified allergen is located within the periplasm and not secreted as taught by the '799 patent. Claim 44 is included in this rejection because it is within the purview of one ordinary skill in the pharmacology art to administer the formulation by rectal administration. The recitation of "dead" *E coli* is an obvious variation of the references teachings.

15. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,888,799 (March 1999, PTO 1449) in view of WO 99/38978 publication (Aug 1999, PTO 1449) as applied to claims 34-36, 38-40, and 42-44 above, and further in view of US Pat No. 5,834,246 (Nov 1998, PTO 892).

The combined teachings of the '799 patent, the WO 99/38978 publication and Yeung et al have been discussed supra.

The claimed invention in claim 41 differs from the teachings of the references only in that the food allergen protein is located in the cytoplasm of the dead *E coli*.

The '246 patent teaches a recombinant system for inducible overexpression of protein such as cholera B-subunit (CTB) with TtacP promoter in *E. coli*. The expression or production of the reference protein CTB is inducible under the control of the reference TtacP promoter and this allows production of high levels of CTB in *E. coli* harboring these plasmids (See column 3, lines 30-39, column 4, Example 1, column 5, lines 63 bridging column 6 lines 1-54, Table 1, in particular). The '246 patent further teaches the recombinant protein CTB is secreted to the

cytoplasm when produced by V. cholerae and then readily be purified in high yield from the culture supernatants (See column 7, lines 43-46, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TtacP promoter for inducible expression of protein at high levels in *E. coli* as taught by the '246 patent for conventional promoter as taught by the '799 patent to produce modified peanut allergens such as Ara h1, Ara h2, Ara h3 or a portion thereof in the cytoplasm as taught by the '246 patent that has a reduced ability to bind and crosslink IgE antibodies as taught by the WO 99/38978 publication and heat killed the *E coli* for a composition comprising dead *E coli* containing modified peanut allergen located in the cytoplasm of the dead E coli as taught by the '799 patent, the WO 99/38978 publication, Yeung et al and the '246 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '246 patent teaches that the TtacP inducible promoter has the advantages of (1) producing the protein of interest at high level without affecting the growth of the microorganisms (See column 3, lines 30-39, column 4, Example 1, column 5, lines 63 bridging column 6 lines 1-54, Table 1, in particular) and (2) the recombinant protein is secreted into the cytoplasm when produced by microorganism such as V. cholerae which then readily be purified in high yield from the culture supernatants (See column 7, lines 43-46, in particular).

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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